DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

DEC 0 8 2000

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(Replaces Reference Numbers: 98-1396 and 98-1395)

Michael Scaife, Ph.D.
Vice President, Regulatory Affairs
Elan Pharmaceuticals
800 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Scaife:

Your Biologics License Application for Botulinum Toxin Type B, "MYOBLOC", for the treatment of cervical dystonia, is approved this date. Elan Pharmaceuticals is hereby authorized to introduce or deliver into interstate commerce, botulinum toxin type B produced at your Neurobloc Production Facility, South San Francisco, CA location under Department of Health and Human Services U.S. License No. 1579.

MYOBLOC is indicated for the treatment of patients with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia. In accordance with approved labeling, your product will bear the tradename MYOBLOC, and will be marketed in 3.5 mL single use vials containing 2500 U, 5000 U or 10,000 U per vial.

Under this authorization you are approved to manufacture MYOBLOC at the Neurobloc Production Facility (NPF) in South San Francisco, CA. Drug product will be shipped to a contract filling and packaging facility, ———————— ———————— for filling, labeling and packaging. Packaged MYOBLOC will be distributed by ———————— ————————

The dating period for this product shall be 21 months from the date of manufacture when stored continuously at 2-8°C. The concentrated and diluted bulk products may each be stored for up to 12 months when stored continuously at 2-8°C. The date of manufacture shall be defined as the date of the last valid potency test on the final container product. This potency test should be initiated within 30 days of the filling date. Any extension of the dating

period will require the submission of supporting data as a supplement to your biologics license application for review and approval. Alternatively, you may submit a stability protocol to be used in extension of dating as a supplement to your license application.

You are requested to submit to the Center for Biologics Evaluation and Research (CBER) samples of future formulated product together with the protocols showing the results of all applicable tests. No lots of product shall be distributed until notification of release is received from the Director, CBER.

We acknowledge your commitments dated November 7, 2000, November 17, 2000, November 21, 2000, and December 7, 2000, for the following postmarketing clinical and manufacturing studies and data:

1. You have agreed to initiate a postmarketing study to evaluate the safety and immunogenicity of MYOBLOC in patients with cervical dystonia. You have made the following commitments for timeframes of conducting the study and submission of related materials to CBER:

    a. The study protocol will be finalized and submitted to CBER for review and comment by February 2001.

    b. The study will be initiated by June 2001.

    c. A total of 500 study subjects will be enrolled.

    d. Enrollment of study subjects will be completed in approximately 3.5 years with the last subject to be entered by December 2004.

    e. All study subjects will be followed until the 2-year clinical observation period for the last enrolled patient is completed in December 2006.

    f. Closure and initiation of analysis of the database will occur in June 2007, with completion of database analysis by November 2007.

    g. The Clinical Study final report will be completed and submitted to CBER by February 2008.

2. [redacted]

3. [redacted]

4. You have agreed to submit a complete testing data report from fermentation through the diluted bulk stage, for the next lot of product manufactured after the concentrated product lot designated D90001 and submission of the completed report by the end of December 2000.

5. You have agreed to perform stability studies on a lot of product in final container manufactured from a new lot of concentrated product (CP) near the end of its dating period. This lot of CP will be manufactured by April 2001 and will be held at 2-8°C for 12 months before compounding the diluted bulk for further manufacture by April 2002. The diluted bulk will be stored for a period of no less than 3 months but no more than 6 months at 2-8°C to simulate the upper limit of storage in routine manufacturing. Stability reports for the final container through the 21 month dating period will be submitted to CBER starting at the 3 month timepoint and then at 6 month intervals through July 2004.

6. You have agreed to monitor stability using one lot of MYOBLOC per year for each fill size (2500 U, 5000 U, and 10,000 U) in accordance with the current stability protocol.

This information will be placed in your biologics license application file for this product.

Changes in the manufacturing process, manufacturing facility, product testing, packaging or labeling for botulinum toxin type B (MYOBLOC) may require the submission of a supplement to your biologics license application for review and approval prior to implementation.

It is required that adverse experience reports be submitted in accordance with the adverse events reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, MD 20852-1448.

It is required that reports of errors and accidents in manufacture be submitted in accordance the error and accident reporting for licensed biological products (21 CFR 600.14). All error and accident reports should be promptly identified according to 21 CFR 600.14 and be submitted to the Director, Office of Compliance, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Please acknowledge receipt of this letter to the Director, Division of Vaccines and Related Products Applications, HFM-475, Center for Biologics Evaluation and Research.

Sincerely yours,

Karen Midthun, M.D.
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

Steven A. Masiello
Director
Office of Compliance and
Biologics Quality
Center for Biologics
Evaluation and Research